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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/22/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-53 and 56-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *42-53 and 56-78* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/22/06 has been entered.

2. Claims 42-53 and 56-78 are pending and under examination.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

Rejection Withdrawn

4. The rejection of claims 42-53 and 56-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn. and re-written below.

5374 2/1/07

New Grounds of Rejection and Response to Arguments

5. Claim 60 is objected to because of the following informalities: The claim recites, "the method of claim 59, X_3X_4 are nucleotides selected from the group....".

Appropriate correction is required such that the claim reads "the method of claim 59, wherein X_3X_4 are nucleotides selected from the group....".

6. Claims 42-53 and 56-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 42-67 are drawn to a method for treating cancer, comprising administering to a human subject an effective amount of a CpG immunostimulatory oligonucleotide having at least one unmethylated CpG dinucleotide, wherein at least one nucleotide of the stabilized CpG immunostimulatory oligonucleotide has a phosphate backbone modification and wherein the oligonucleotide is 8 to 100 nucleotides in length, further comprising administering a chemotherapeutic agent, further comprising administering a cancer immunotherapeutic agent, wherein the cancer is brain cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, colon cancer, leukemia, carcinoma, sarcoma; further wherein the phosphate backbone is a phosphorothioate modification, wherein the oligonucleotide includes the phosphate backbone modification on the 5' inter-nucleotide linkages, 3' inter-nucleotide linkages, further wherein the oligonucleotide comprises 5' $X_1X_2CGX_3X_4$ 3', wherein X_1X_2 and X_3X_4 are nucleotides wherein X_3X_4 are nucleotides selected from the group consisting of: TpT and TpC, further wherein X_1X_2 are GpA and X_3X_4 are TpT, further wherein X_1X_2 are both purines and X_3X_4 are both pyrimidines, further wherein X_1X_2 are GpA and X_3X_4 are pyrimidines, further wherein the oligonucleotide is 8 to 40 nucleotides in length. further

wherein 5' $X_1X_2CGX_3X_4$ 3' is not palindromic, further wherein the CpG immunostimulatory oligonucleotide includes at least two CpG motifs, further wherein at least one of the at least two CpG motifs is not palindromic. The claims are further drawn to the above-mentioned method wherein the oligonucleotide is administered prior to a chemotherapy, administered subcutaneously, administered with an antibody for antibody dependent cellular cytotoxicity. In addition, the claims are drawn to a method for treating NSLC in a human subject administering to a human subject having NSCLC an effective amount to treat NSCLC of an immunostimulatory oligonucleotide that includes at least one unmethylated CpG dinucleotide, wherein the immunostimulatory oligonucleotide includes a phosphate backbone modification and, wherein the oligonucleotide is 8 to 100 nucleotides in length, further comprising administering a chemotherapeutic agent, an immunotherapeutic agent, wherein the phosphate backbone is a phosphorothioate modification, wherein the oligonucleotide is 8 to 40 nucleotides in length, wherein the CpG immunostimulatory oligonucleotide includes at least two CpG motifs, wherein at least one of the at least two CpG motifs is not palindromic and further wherein the oligonucleotide is administered subcutaneously.

However, the specification provides insufficient guidance and objective evidence that such stabilized CpG immunostimulatory oligonucleotide would predictably treat cancer. The specification provides no guidance on the administration of the claimed oligonucleotide in vivo.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The nature of the invention:

The claims have been described supra. Therefore the general nature of the invention is cancer therapy comprising administering to a subject an effective amount of a stabilized CpG immunostimulatory oligonucleotide, further comprising administering a chemotherapeutic and/or a immunotherapeutic agent.

The breadth of the claims:

The breadth of the claims is very broad. For instance the claims encompass the treatment of various cancers comprising administering CpG dinucleotide.

The unpredictability of the art and the state of the prior art:

It is noted that the claims encompasses a method for treating cancer comprising administering a CpG dinucleotide to a subject, thus the claims embrace a multitude of CpG dinucleotides that have 8-100 nucleotides in length and have a phosphate backbone modification which is a phosphorothioate modification.

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule.

For instance, Agarwal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (see page 119 "concluding remarks" in particular). In addition, Agarwal et al teach that eventhough significant progress has been made in understanding the immunological and pharmacological affects, only limited data are available on optimized CpG DNA agents in human clinical trials (page 116 2nd column, CpG DNA in clinical trials).

Further, the unpredictability in the treatment of cancer is very high as pointed out by Peterson et al, Schuh et al, Bibby et al and Saijo et al (please see pages 7-12 of the previous office action mailed on 07/19/2006), who teach that numerous agents, even after showing activity in preclinical models, had minimal clinical activity; and that the preclinical data does not always predict success in clinical trials.

Working Examples and Guidance in the Specification

The specification has no working examples indicating any CpG immunostimulatory oligonucleotide comprising an unmethylated CpG motif can be useful for treating any kind of cancer.

Quantity of Experimentation

Considering the breadth of the claims and lack of working examples and guidance in the specification, one of skill in the art would be required to perform

additional experimentation in order to be able to effectively use the invention with a reasonable expectation of success. Considering the teaching in the art and lack of examples and guidance in the specification, one of skill in the art could not use the claimed CpG-containing oligonulceotides comprising at least one unmethylated CpG motif and has a phosphorothioate modified backbone. However, additional experimentation would be required in order to show that CpG-containing oligonucleotide is effective in treating any type of cancer. The amount of additional experimentation is deemed to be undue because in order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonulceotides would not work for treating or preventing any cancer.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering 1) the high degree of unpredictability recognized in the art, particularly the required characteristics of the immunostimulatory oligonucleotide in order to be an effective in vivo immunostimulatory oligonucleotide; 2) the breadth of the claims as mentioned above; 3) the limited number of working examples and guidance in the specification; and 4) the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

The applicants argue that the examiner has not provided evidence to support the statement "there exists a high unpredictability of using CpG molecules in the treatment of cancer in humans" (page 3, in particular). Further, the applicants state that inventors provided significant amounts of data testing many CpG containing dinucleotide ..... evidence in the application clearly established a pattern of immune stimulation by this class of oligonucleotides which was consistent with the treatment of cancer (pages 4-6 of the arguments, in particular). Applicants also state that the teachings of Agarwal et al do not call into question that one of skill in the art would have accepted the teachings of the specification made by applicants at the time the patent application was filed. Applicants also argues that it is not clear as to how the statement cited by the Examiner render the use of CpG oligonucleotides in the treatment of cancer highly unpredictable.

The specification only discloses the induction of cytokines such as IL-6, IL-12 and IFN-gamma, and not the treatment of cancer comprising administering CpG dinucleotides, which is the invention as claimed. While it is noted that Agarwal et al teach the pattern and kinetics of the induction of cytokine, Agarwal et al clearly suggest the undue experimentation needed in the enablement of treatment methods using CpG-containing oligonucleotides. For example, Agarwal et al teach that even though significant progress has been made in understanding the immunological and pharmacological affects, only limited data are available on optimized CpG DNA agents in human clinical trials (page 116 2nd column, CpG DNA in clinical trials). Further, Agarwal et al also affirm that the pattern and kinetics of induction of the cytokines in vivo

depends on the sequences flanking the CpG dinucleotide, as well as the dose and the route of administration which are not yet known. Thus, if the unpredictability exists at the time of the studies performed by Agarwal et al (in 2002), one of skill in the art would readily envisage the unpredictability that exists in the enablement of the claimed invention at the time of filing of the instant application (in 1994). Agarwal et al also suggest that the medicinal chemistry of CpG DNA have just begun and needs further fine-tuning, which clearly indicates that at the time of filing of the instant application the applicants were not enabled for the claimed invention, which is a method of treating various cancers comprising administering CpG immunostimulatory oligonucleotides.

The applicants further state that Agarwal et al simply express an opinion and is not sufficient to demonstrate lack of enablement. It is the examiner's position that Agarwal et al concluded the unpredictability in treatment of cancer comprising administering CpG dinucleotide only after a series of experimental studies as discussed in the publication. As such, if the applicant considers Agarwal et al merely as an opinion, it is the examiners position that the applicants statement "the treatment of cancer comprising administering CpG dinucleotide is enabled by the specification" is also merely a contemplation because the specification does not show any evidence as to the treatment of cancer. The showing of induction of three cytokines by a molecule does not enable one skill in the art for treatment of cancer comprising administering such molecule. The molecular mechanisms that are involved in the progression of cancer and further inhibiting the cancer growth thus leading to the treatment of cancer

requires a showing of such or a correlation between the in vitro studies to in vivo treatment regimens. As disclosed, the specification does not provide any such information.

Further, the data presented in the specification, in contrary to the applicant's statement, does not provide significant data testing many CpG containing dinucleotide for the treatment of cancer. It is noted that the specification established a pattern of immune stimulation by this class of oligonucleotides, and it is also noted that the induction of cytokines may be involved in the cancer regression – however, the correlation between the induction of the three disclosed cytokines and treatment of cancer has not been clearly established.

Applicants further argue that human clinical trial data is not required for a complete specification and that applicants have described the data included in the specification and asserted that it correlates.

While human clinical data is not needed, applicant does need to provide sufficient evidence to enable the claimed invention as stated in the rejection because there is no correlation between the claimed invention and the working examples. The unpredictability in the art of treatment of cancer requires for a proper analysis of a cancer therapeutic agent in vivo and in vitro. The specification has no working examples indicating any CpG immunostimulatory oligonucleotide comprising an unmethylated CpG motif can be useful for treating any kind of cancer. If the applicant is under the impression that the specification does in fact provide a correlation between

the scope of the claims and the scope of the enablement set forth, statements indicating the specific portions of the specification that provide such information is requested.

The applicant argues that the references cited by the Examiner are to establish that pre-clinical work is not always predictive of clinical success and the law is well established that a clinical trial is not required for enablement and that it is not appropriate for the PTO to determine if a drug is clinically successful (page 9 of the arguments, in particular).

While it is agreed that the PTO does not require the clinical success of a drug, it should be noted that PTO requires the enablement of the claimed invention. In the instant case, the claims are drawn to a method of treatment of cancer. Based on the unpredictability that exists in treatment of cancers, it is necessary to show the correlation of the working examples with the claimed invention. The studies as disclosed in the specification do not support this theory because neither the specification nor prior art describe a direct correlation between induction of cytokines and treatment of cancer. Further, the prior art as cited before clearly shows the unpredictability that exists in the treatment of cancer. In addition, the specification only shows the induction of cytokines in vitro and the extrapolation of such results into treatment of cancer is merely a contemplation. In addition, the applicant is pointed to the teachings of Zips et al (page 3 column 2, in particular), which state, "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-

malignant cells. Vascularisation, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential."

Thus, The instant application gives no data relevant to the use of the nucleic acids mentioned in the claims in any in vivo method to control or affect any of the conditions mentioned in the claims. One skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids. For example, the instant application does not give guidance as to the type of administration, the times or frequencies of administration, or the dosages required to obtain desired effects.

Conclusion

5. No claims are allowed

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

8. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

SHEELA HUFF
PRIMARY EXAMINER